No new matter has been introduced by this Amendment. Support for the phrase "wherein the polypeptide has the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide" can be found in the specification on page 11, lines 14-19 which states:

> "*The FBD commences at amino acid number 1 of mature fibronectin, which is glutamine and corresponds to the fourth amino acid (G) shown in Figure 1A, i.e., the N-terminus of the FBD sequence is Q-A-Q-Q (glutamine-alanine-glutamine-glutamine).*"

The specification discloses three species of imaging agents comprising fibrin binding domain polypeptides of molecular weight of 31 kD, 20 kD and 12 kD, *inter alia* on page 47, lines 10-15. The applicant therefore may claim imaging agents comprising polypeptides of molecular weight less than 31 kD, which is encompassed in the phrase "wherein the polypeptide has a molecular weight less than 31 kD" in claim 1 as now amended.

Furthermore, support for the phrase "wherein the polypeptide has a molecular weight less than 31 kD" can be found in the specification on page 41, lines 26-27 which states:

> "*These smaller polypeptides are smaller than 31 kD and comprise part of the sequence of the fibrin binding domain.*"

Thus applicants maintain that no issue of new matter exists and respectfully request entry of this Amendment.

Furthermore, the subject invention is novel and inventive, as the prior art does not disclose or suggest an imaging agent which comprises a polypeptide labeled with an imageable marker, such polypeptide having an amino acid sequence which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronectin, wherein the polypeptide has the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD, and wherein the imaging agent binds to fibrin.

Applicants will now relate to the Examiner's objections in the order set forth in the February 14, 2001 Office Action.

Claim Rejections 35 U.S.C. § 112 (first paragraph)

The Examiner has rejected claims 88-96 because the specification while being enabling for the fibronectin fragments disclosed in the specification, allegedly does not reasonably provide enablement for any portion of fibronectin. The Examiner stated that the specification does not enable a person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claims.

The Examiner further stated that the specification on page 53 describes three purified polypeptides, having molecular weights of 31 kD, 20 kD and 12 kD derived from the first 262 amino acids of the N-terminal sequence of fibrin binding domain of fibronectin, but that the specification does not define the one fifth portion of the N-terminal sequence nor any correlation between the one fifth portion of sequence with the sequences from where the 31 kD, 20 kD and 12 kD polypeptides were derived.

The Examiner further stated that it would require undue experimentation for one of ordinary skill in the art to determine all possible imaging agents derivable, having at least one fifth of the amino acid sequence of the N-terminal region of fibrin binding domain of fibronectin, since a large number of such polypeptides is easily envisioned but the determination of biological activity of all such polypeptides, each requiring purification, refolding and labeling, is well outside the realm of routine experimental work.

The Examiner further stated that the specification lacks guidance as to exactly what polypeptides might possess the claimed activity, and that one of ordinary skill in the art would require guidance as to what region of fibronectin is included in the phrase the "fibrin binding domain", what specific amino acids are encompassed and what is the sequence.

In response, claim 88 as amended hereinabove is directed only to an

imaging agent which comprises a polypeptide labeled with an imageable marker, such polypeptide having an amino acid sequence which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronectin, wherein the polypeptide has the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD, and wherein the imaging agent binds to fibrin.

Claim 88 as now amended specifically defines the characteristics of the fibrin binding domain polypeptide comprising the claimed imaging agent, such that one of average skill in the art would be able to make and use the invention. Furthermore, the invention as now claimed is fully enabled by the specification.

To be more specific, claim 88 as amended recites that the amino acid sequence of the N-terminus of the subject polypeptide is gln-ala-gln-gln or met-gln-ala-gln-gln, and that the amino acid sequence of the subject polypeptide corresponds to at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronectin. The specification states *inter alia* on page 47, lines 10-15, that a 31 kD polypeptide corresponding to an amino acid sequence present in the fibrin binding domain and having the amino acid sequence of amino acids 1-262 as shown in Figure 1 is the full length fibrin binding domain of human fibronectin. Amino acid residues 1-4 of the native fibrin

binding domain correspond to the sequence gln-ala-gln-gln as shown in Figure 1 and explained on page 11, lines 14-19.

Hence, one of ordinary skill in the art would be able to readily calculate that one fifth of 262 amino acids corresponds to about 52 amino acids, and would thus understand that the minimum length of the subject polypeptide comprising the claimed imaging agent is 52 amino acids. Further, one skilled in the art would understand that the amino acid sequence of the subject polypeptide comprising at least 52 amino acids could not be randomly chosen from any portion within the fibrin binding domain, but must begin with the N-terminus of the native fibrin binding domain i.e. gln-ala-gln-gln, or met-gln-ala-gln-gln as recited in claim 88. Thus, the polypeptide comprising the claimed imaging agent corresponds to at least amino acid residues 1-52 of the fibrin binding domain and encompasses the range of progressively longer polypeptides derived from the fibrin binding domain, such that the maximal such length corresponds to a polypeptide of molecular weight less than 31 kD. There is now clear correlation between the one fifth portion of the binding domain and its N-terminal amino acid sequence.

M.P.E.P § 2164.03 provides that "...even in unpredictable arts, a disclosure of every operable species is not required." Since the subject application includes a disclosure of three operable examples of the claimed invention (i.e. a 20 kD polypeptide in Example 2 and the 12 kD and 12 kD' polypeptides in Example 9),

applicants maintain that they are entitled to the scope of the claims now pending as amended above.

Furthermore, applicants should not be forced to limit their claims to the specific imaging agent disclosed in the specification i.e. the 12 kD, 12kD' 20 kD and 31 kD polypeptides, since they were the first to disclose a polypeptide imaging agent corresponding to a fragment of the N-terminal fibrin binding domain of fibronectin. In particular, applicants are entitled to claim a polypeptide imaging agent which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronectin, wherein the polypeptide has the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD, and wherein the imaging agent binds to fibrin.

The Examiner's attention is directed to U.S. v. Telectronics Inc., 8 USPQ2d 1217, 1222, 1223 (Fed. Cir. 1988), a copy of which is attached hereto as **Exhibit B**, where it was stated:

" A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive."

* * *

"Since one embodiment is admittedly disclosed in the specification,

along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation. *See SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed. Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention); *Hybritech Inc.*, 802 F.2d at 1384, 231 USPQ at 94 (the enablement requirement may be satisfied even though some experimentation is required)."

Applicants are entitled to generic claims such as claims 88-96. Legal authority supporting the grant of claims of such scope is provided by In re Angstadt and Griffin, 190 USPQ 214, 218 (CCPA 1976) a copy of which is attached hereto as **Exhibit C**:

" Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalysts which will not work. The question, then, is whether in an unpredictable art, section 112 required disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with 'thousands' of examples or the disclosure of 'thousands' of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor

seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid 'literal' infringement of such claims by merely finding another analogous catalyst complex which could be used in 'forming hydroperoxides'." (Emphasis in original).

Applicants note that claims 88-96 recite a polypeptide imaging agent which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronectin, wherein the polypeptide has the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD, and wherein the imaging agent binds to fibrin. Applicants respectfully submit that their teachings and exemplifications enable a person of ordinary skill in the art to practice the invention of claims 88-96.

In view of the amendment of the claims and the preceding comments, the Examiner is respectfully requested to withdraw the rejection of the claims under 35 U.S.C. § 112 (first paragraph).

Claim Rejections 35 U.S.C. § 112 (second paragraph)

The Examiner has rejected claims 88-96 as being indefinite for

failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner states that it is not clear from claim 88 or the specification what is the corresponding amino acid sequence which comprises at least one fifth portion of the amino acid sequence of the N-terminal region of the fibrin binding domain of fibronectin.

The Examiner further states that the word "capable" is not clear, since it is not clear whether the agent actually needs to bind the fibrin of merely have the capability to do so.

In response, claim 88 has been amended hereinabove to encompass a fibrin binding domain polypeptide imaging agent which comprises at least one fifth of the amino acid sequence of the N-terminal fibrin binding domain of naturally-occurring fibronectin, wherein the polypeptide has the amino acid sequence gln-ala-gln-gln or met-gln-ala-gln-gln at the N-terminus of the polypeptide, and wherein the polypeptide has a molecular weight less than 31 kD, and wherein the imaging agent binds to fibrin.

The amendment provides a clear correlation between the one fifth portion of the fibrin binding domain polypeptide and its N-terminal amino acid sequence, as hereinbefore discussed.

In response to the Examiner's comments regarding the word "capable", claim 88 has been amended by deletion of the word "capable", as

suggested by the Examiner.

In view of the amendment of the claims and the preceding comments, the Examiner is respectfully requested to withdraw the rejection of the claims under 35 U.S.C. § 112 (second paragraph).

Double Patenting

The Examiner has rejected claims 88 and 95 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,270,030 in view of Baralle (EP 0,207,751 A1), Hynes et al.

The Examiner has rejected claims 88-96 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,121,426 in view of Baralle (EP 0,207,751 A1), Hynes et al.

The Examiner has rejected claims 88-96 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,965,383 in view of Baralle (EP 0,207,751 A1), Hynes et al.

In response, applicants herewith submit as **Exhibit D,** a terminal disclaimer with respect to U.S. Patent Nos. 5,270,030, 5,965,383 and 6,121,426. A copy of Assignment from Tikva Vogel, Avigdor Levanon, Moshe Werber, Rachel Guy and Amos Panet, recorded at the

United States Patent and Trademark Office on July 23, 1990, at Reel No. 5383, Frames 508-510, is attached hereto as **Exhibit 1**, in connection with U.S. Serial No. 07/526,397 to which the subject application claims benefit under 35 U.S.C. §120 as a continuation.

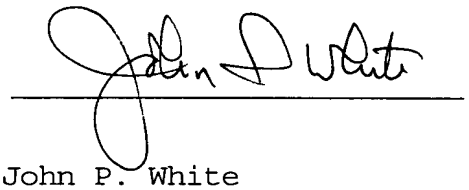
In view of the amendments and preceding remarks, applicants request that the Examiner reconsider and withdraw the rejection of the claims now pending in this action and allow these claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $890.00 fee for a three-month extension of time is deemed necessary in connection with the filing

of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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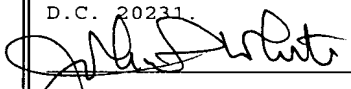
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



8/14/09

John P. White Date
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